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SYNTHESIS, PHYSICOCHEMICAL AND ANTICONVULSANT PROPERTIES OF SOME N–SUBSTITUTED AMIDES OF 3–SPIROCYCLOALKYLPYRROLIDINE–2,5–DIONE

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Abstract: The synthesis and physicochemical properties of new derivatives of N–benzyl and N–phenyl amides of 2–(3–spirocyclohexanepyrrolidine–2,5–dione) acetic acid, 4–(3–spirocyclohexanepyrrolidine–2,5–dione) benzoic acid and 4–(3–spirocyclopentanepyrrolidine–2,5–dione) benzoic acid are described. N–substituted amides were prepared by condensing the obtained acids with the corresponding phenyl– or benzylamine derivatives in DMF, in the presence of the N,N–carbonyldiimidazol (CDIM) reagent at room temperature. The compounds were evaluated for anticonvulsant activity. The portion coefficients were calculated using the Prolog P module of the Pallas system. The structure of the new amides was confirmed by elemental and spectral analyses.

Keywords: N–substituted amides of 3–spirocycloalkylpyrrolidine–2,5–dione, spirosuccinimides, lipophilicity, anticonvulsant properties

A great number of compounds are synthesized every year to determine their anticonvulsant properties. It is well known that 4–, 6–heterocycle rings, one or two carbonyl groups, as well as an aromatic system are required to assess their anticonvulsant activity (1,2). Among the compounds investigated for anticonvulsant activity, one of the structures is an amide fragment. The amide function has been found in many new compounds with potent anticonvulsant activity such as ameltolide (3), rufinamide, remacemide, seretolide, harkoserid and cerabersat (4) (Figure 1).

Structure–activity relationships of the described amides have shown that the substitution pattern and the kind of substituents in an aromatic ring are very important for anticonvulsant activity. Methyl groups and fluor atoms in the aromatic ring seem to be essential here.

Studies carried out by Scott at al. (5, 6) on a group of spiro[4,5] and spiro[4,6] carboxyl acids as cyclic analogues of valproic acid demonstrated anticonvulsant activity of those compounds. Further investigation of a group of spiro succinimides (7) as well as crystallographic data (8) showed a key role of the cyclic system connected with the imide fragment through a spiro carbon atom regarding the influence of compounds of that type on anticonvulsant activity.

The lipophilic character was demonstrated in many types of drug action. It was found that the maximum potency of drugs acting on the central nervous system was obtained for congeners with an optimum lipophilicity close to 2. Lien (9) reported that the anticonvulsant activity of different types of compounds was correlated with their lipophilicity.

In the present study, we determined clog *P* values for all the obtained amides using the Prolog P module of the PALLAS system (10). The correlation between the clog *P* values of anticonvulsant drugs with amide fragment and our new compounds **I, IV–XII** is presented in Table 5.

In recent years, we have synthesized a great number of compounds with anticonvulsant activity by changing substituents in position 1 and 3 of the pyrrolidine–2,5–dione nucleus. Some of them were very effective in anti–MES and sc. Met tests (11–14). These findings and the information given in the introduction have prompted us to carry out synthesis of new derivatives of 3–spirocycloalkylpyrrolidine–2,5–dione with an amide fragment separated from the imide nitrogen atom by the methylene group [**IV–VII**] or the phenyl ring [**VIII–XII**].

1–Carboxy–1–cyclohexaneacetic acid and 1–carboxy–1–cyclopentaneacetic acid, obtained by the previously described method (5,12), were used as starting materials. 4–(3–spiro–cyclohexanepyrrolidine) benzoic acid [**II**] and 4–(3–spirocyclopentanepyrrolidine–2,5–dione) benzoic acid [**III**] were synthesized by El–Talbany et al. (15,16) and also used as starting materials. In this study, 2–(3–spirocyclohexanepyrrolidine–2,5–dione) acetic acid [**I**], 4–(3–spirocyclohexanepyrrolidine–2,5–dione) benzoic acid [**II**] and 4–(3–spirocyclopentane–

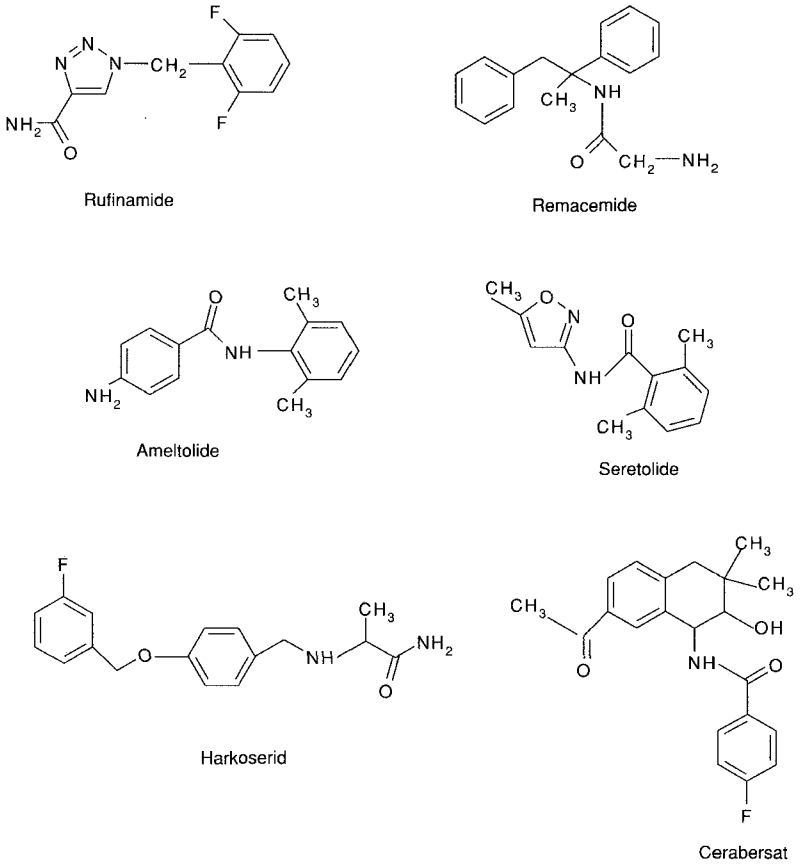


Figure 1. Chemical structures of potent anticonvulsant compounds with amide function.

pyrrolidine–2,5–dione)–benzoic acid [**III**] were synthesized according to the procedures shown in Scheme 1.

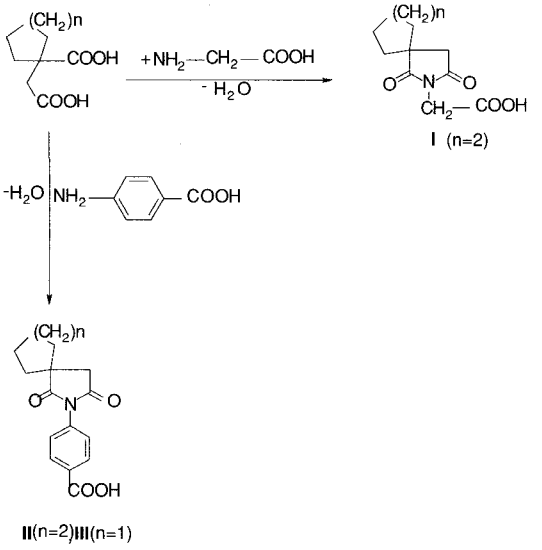
The obtained acids [**I, II, III**] were used to synthesize new N–benzyl– or N–phenyl– amides of 3–spirocyclohexanepyrrolidine–2,5–dione–1–acetic acid [**IV–VI**], 3–spirocyclohexanepyrrolidine–2,5–dione–1–(4–carboxy)–benzoic acid [**VII–X**] and 3–spirocyclopentanepyrrolidine–2,5–dione –1–(4–carboxy)–benzoic acid [**XI, XII**]. The amides [**IV–XII**] were prepared by condensing the above acids [**I, II, III**] with the corresponding amine in DMF in the presence of carbonyldiimidazol (CDIM), yielding 75–80% (17) (Scheme 2).

^{1}H NMR and MS spectra of the synthesized compounds were studied.

In the MS spectra, the peaks of molecular ions [M^++1] were clearly detectable for compounds **IV, VIII–XII** (intensity ranging from 82 to 100%). For compounds **V–VII,** the peaks of molecular ions [M^++1] were within the range of 21–27% intensity. The characteristic ions M^+ 93 (100%), 107 (100%), 124 (100%) and M^+ 208 (1–15%) confirmed the fragmentation of the amide bond in compounds **IV–VI.** The ion M^+ 270 (65–100%) was characteristic of compounds **VII–X** as a peak resulting from the fragmentation of the amide bond. In amides **XI, XII,** the ion M^+ 256 (56% and 60%) also confirmed the fragmentation of amide bond. The other peaks of ions M^+ 95 (3–18% and M^+ 81 (12–15%) confirmed the fragmentation of 3–spirocyclohexane–pyrrolidine–2,5–dione [**IV–X**] and 3–spirocyclopentanepyrrolidine–2,5–dione [**XI, XII**] rings. All the characteristic ions agreed with the proposed structures.

The ^{1}H NMR spectra revealed there a few characteristic chemical shifts of the investigated amides. The chemical shifts of pyrrolidine–2,5–dione protons in all the compounds studied were shown as singlets at δ 2.64 ppm and δ 2.75 ppm, which were raised upfield by 0.03 ppm and 0.02 ppm, respectively. The resonance signal of $-CH_2$ between the imide nitrogen and the amide bond [**IV–VI**] appeared as a singlet at δ 4.29 ppm. The resonance signal of $-CH_2$ benzyl group appeared as a dublet at δ 4.30–4.45 ppm [**V, I**] and δ 4.57–4.65

ppm [**VIII–XII**]. The signal of the N–H proton of amide group occurs as a singlet at δ 5.99 ppm [**V, VI**] and as a triplet at δ 6.33 ppm–δ 7.18 ppm for amides **IV, VII–XII**. The chemical shifts of the cyclohexane ring were within the range of δ 1.21–1.96 ppm [**IV–X**] and of the cyclopentane ring within the range of δ 1.57–2.27 ppm. The signals of aromatic protons for all the compounds occurred as multiplets within the range of δ 6.85–7.88 ppm.

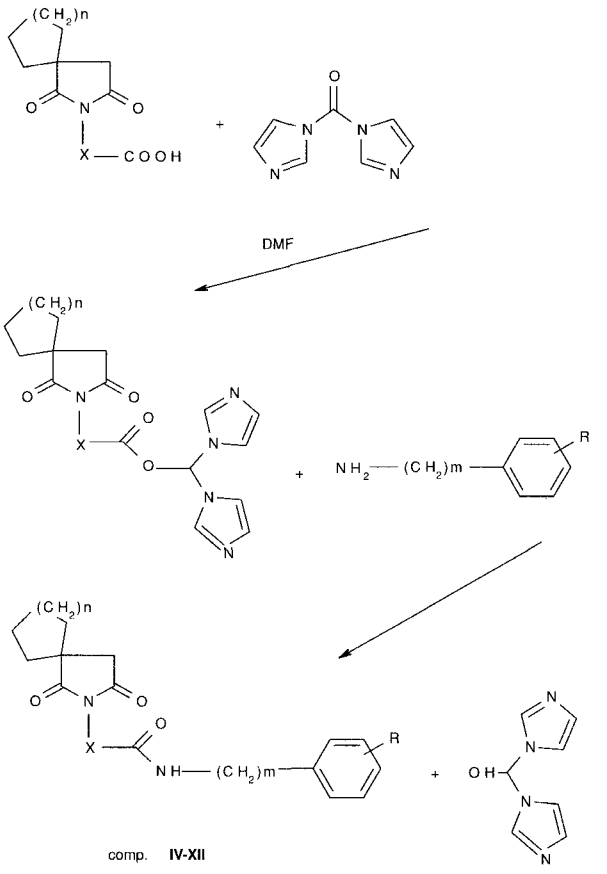


Scheme 1.

EXPERIMENTAL

Chemistry

Melting points (^{0}C) were left uncorrected. ^{1}H–NMR spectra were obtained on a Varian Mercury spectrometer working at 300 MHz. Chemical shifts were described as parts per million (δ ppm); $(CH_3)_4Si$ (TMS) was used as an internal standard.



No.	IV	V	VI	VII	VIII	IX	X	XI	XII
n	2	2	2	2	2	2	2	1	1
X	$-CH_2$	$-CH_2$	$-CH_2$	$-C_6H_4$	$-C_6H_4$	$-C_6H_4$	$-C_6H_4$	$-C_6H_4$	$-C_6H_4$
m	0	1	1	0	1	1	1	1	1
R	H	H	4–F	H	4–F	2–OCH_3	4–OCH_3	H	2–OCH_3

Scheme 2.

Table 1. Experimental data of compounds **I–III**

No.	Molecular Formula Weight	Yield Mp.[^{0}C]	Analyses			R_f[a]	^{1}H NMR[b] δ (ppm)/DMSO
			%C	%H	%N		
I	$C_{11}H_{15}O_4N_1$ 225.25	88.7 106–108	58.72 58.87	6.72 6.50	6.23 6.20	0.86 A 0.69 B	1.27–1.85 (10H, m, cyclohexane), 2.62 (2H, s, $-CH_2$ imide), 4.26 (2H, s, CH_2), 12.5 (1H, s, COOH)
II	$C_{16}H_{17}O_4N_1$ 287.32	83.8 244–246	66.96 66.73	5.97 5.89	4.88 4.89	0.93 A 0.90 B	1.21–1.73 (10H, m, cyclo–hexane), 2.74 (2H, s, $-CH_2$ imide), 7.39–7.91 (2H, aromat), 8.00–8.04 (2H, aromat), 13.09 (1H, br.s, COOH)
III	$C_{15}H_{15}O_4N_1$ 273.29	85.6 192–194	66.00 66.24	5.54 5.62	5.13 5.25	0.88 A 0.85 B	1.64–2.01 (8H, m, cyclo–pentane), 2.79 (2H, s, $-CH_2$ imide), 7.41–7.45 (2H, aromat), 8.00–8.04 (2H, aromat), 13.10 (1H, br.s, COOH)

[a] Solvents: A) chloroform : methanol : acetic acid (60 : 10 : 5) , B) butanol : acetic acid : water (5 : 4 : 1)
[b] Compound **I** in $CDCl_3$

Table 2. Physical and analytical data for compounds **IV–XII**

No.	Molecular Formula Weight	Yield Mp.[^{0}C]	Analysis			R_f[a]
			%C	**%H**	**%N**	
IV	$C_{17}H_{20}O_3N_2$ 300.36	78 82–84	68.06 67.73	6.72 6.80	9.34 8.94	0.63 A 0.80 B
V	$C_{18}H_{22}O_3N_2$ 314.39	58 178–180	68.85 69.06	7.06 7.03	8.92 8.97	0.59 A 0.75 B
VI	$C_{18}H_{21}O_3N_2F_1$ 332.38	76 192–194	65.12 64.87	6.57 6.48	8.44 8.28	0.51 A 0.92 B
VII	$C_{22}H_{22}O_3N_2$ 362.43	81 230–232	73.00 72.72	6.13 6.07	7.74 7.69	0.71 A 0.90 B
VIII	$C_{23}H_{23}O_3N_2F$ 394.45	75 176–178	70.12 69.96	5.88 5.88	7.11 7.01	0.58 A 0.87 B
IX	$C_{24}H_{26}O_4N_2$ 406.48	81 206–208	71.00 71.07	6.45 6.46	6.90 6.82	0.64 A 0.84 B
X	$C_{24}H_{26}O_4N_2$ 406.48	84 158–160	71.00 70.90	6.45 6.48	6.90 6.87	0,42 A 0,87 B
XI	$C_{22}H_{22}O_3N_2$ 362.43	78 140–142	73.00 72.65	6.13 6.08	7.74 7.72	0,64 A 0,94 B
XII	$C_{23}H_{24}O_4N_2$ 392.46	68 104–106	70.47 70.24	6,17 6.17	7.15 7.05	0,35 A 0,91 B

[a] Solvents: A– benzene : ethyl acetate: aceton (10 : 5 : 1), B– butanol : acetic acid : water (5 : 4 : 1)

Signal multiplicities were given the following abbreviations: s (singlet), d (doublet), dd (double doublet), q (quartet), m (multiplet). Mass spectra (EI) were measured on a 95 MATS Sigimann spectrometer. Elemental analyses of C, H, N were within ±0.4% of the theoretical values. The purity of the compounds was checked by thin–layer chromatography (TLC) performed on Merck silica gel GF_{254} aluminium sheets, using the following developing systems:

A – benzene : ethyl acetate : acetone (10 : 5 : 1), B– butanol : acetic acid : water (5 : 4 : 1). Spots were detected by means of their absorption under UV light, and by visualization with 0.05 mol I_2 in 10 % HCl.

GENERAL PROCEDURE FOR PREPARING 3–SPIROCYCLOHEXANEPYRROLIDINE–2,5–

Table 3. ^{1}H NMR and MS spectral data of compounds **IV–XII**

No.	^{1}H NMR δ (ppm)/ $CDCl_3$	EIMS *m/z* (% intensity)
IV	1.28–1.86 (10H, m, cyclohexane), 2,64 (2H, s, imide),4.29 (2H, s,CH_2), 7.07–7.11 (1H, t, NH, *J*=7.15), 7.28–7.66 (5H, m, aromat.)	300 [M$^+$+1] (82), 208 (15), 180 (57), 152 (14), 95 (13), 92 (100).
V	1.23–1.86 (10H, m, cyclohexane), 2.61 (2H, s, imide), 4.15 (2H, s,CH_2), 4.30–4.45 (2H, d, CH_2–benzyl *J*=5.77), 5.92 (1H,s, NH), 7.24–7.36 (5H, m, aromat.)	314 [M$^+$+1] (27), 180 (7), 106 (100), 92 (18)
VI	1.21–1.87 (10H, m, cyclohexane), 2.61 (2H, s, imide), 4.14 (2H, s,CH_2), 4.38–4.40 (2H, d, CH_2–benzyl, *J*=5.77), 5.99 (1H,s, NH), 6.96–7.25 (4H, m, aromat.)	332 [M$^+$+1] (26), 208 (11), 180 (17), 124 (100), 109 (20), 95 (14).
VII	1.21–1.96 (10H, m, cyclohexane), 2.75 (2H, s, imide), 7.13–7.18, (1H, m, NH), 7.26–7.96 (9H, m, aromat.)	362 [M$^+$+1] (21), 270 (100), 146 (20), 95 (4), 92 (2)
VIII	1.21–1.94 (10H, m, cyclohexane), 2.73 (2H, s, imide), 4.59–4.61 (2H, d, CH_2–benzyl, *J*=5.5Hz), 6.43 (1H, s, NH), 6.99–7.88 (8H, m, aromat.)	394 [M$^+$+1] (100), 270 (77), 124 (7), 95 (4)
IX	1.35–1.95 (10H, m, cyclohexane), 2.72 (2H, s, imide), 3.87 (3H, s, OCH_3), 4.62–4.64 (2H, d, CH_2–benzyl, *J*=5.77Hz), 6.65–6.68 (1H, t, NH, *J*=5.22Hz) 6.88–7.85 (8H, m, aromat.)	406 [M$^+$+1] (97), 270 (65), 136 (100), 95 (5).
X	1.33–1.94 (10H, m, cyclohexane), 2.72 (2H, s, imide), 3.80 (3H, s, OCH_3), 4.56–4.58 (2H, d, CH_2–benzyl, *J*=5.5Hz), 6.33–6.35 (1H, t, NH, *J*=5.55Hz) 6.85–7.88 (8H, m, aromat.)	406 [M$^+$+1] (100), 270 (51), 136 (19), 95 (2)
XI	1.57–2.25 (8H, m, cyclopentane), 2.75 (2H, s, imide), 4.63–4.65, (2H, d, CH_2–benzyl, *J*=5.77Hz), 6.45–6.48 (1H, t, NH, *J*=4.95Hz) 7.27–7.88 (8H, m, aromat.)	362 [M$^+$+1] (100), 256 (56), 105 (17), 90 (12), 81 (15)
XII	1.75–2.27 (8H, m, cyclopentane), 2.75 (2H, s, imide), 3.79 (3H, s, OCH_3), 4.56–4.57, (2H, d, CH_2–benzyl, *J*=5.77Hz), 6.36–6.39 (1H, t, NH, *J*=4.95Hz) 6.85–7.87 (8H, m, aromat.)	392 [M$^+$+1] (100), 256 (60), 240 (4), 136 (19), 121 (14), 81 (12)

DIONE–1– ACETIC ACID [**I**], 3–SPIROCYCLOHEXANEPYRROLIDINE–2,5–DIONE–1–(4–CARBOXY) BENZOIC ACID [**II**], AND 3–SPIROCYCLOPENTANEPYRROLIDINE–2,5–DIONE–1–(4–CARBOXY) BENZOIC ACID [**III**].

To a suspension of 2–cyclohexane–2–carboxy acetic acid or 2–cyclopentane–2–carboxy acetic acid (0.04 mole) in 25 ml of water 2–aminoacetic acid or 4–aminobenzoic acid (0.04 mole) were gradually added. The mixture was heated in an oil bath with simultaneous distillation of water. After complete removal of water, the temperature of reaction mixture was raised up to 190–200^{0}C and maintained for 1.5 h. The precipitated crude product was recrystallized from 96% ethanol. Physicochemical data, ^{1}H–NMR spectral data, yields, elemental analysis and R_f values are presented in Table 1.

GENERAL PROCEDURE FOR THE PREPARATION OF N–BENZYLAND N–PHENYLAMIDES OF 3–SPIRO–CYCLOHEXANEPYRROLIDINE–2,5–DIONE–1– ACETIC ACID [**IV–VI**], 3–SPIROCYCLOHEXANEPYRROLIDINE–2,5–DIONE–1– BENZOIC ACID [**VII–X**] AND 3–SPIROCYCLOPENTANEPYRROLIDINE–2,5–DIONE–1– BENZOIC ACID [**XI–XII**].

The obtained acids [**I, II, III**] (0.02 mole) were dissolved in 20 ml of DMF, and N,N–carbonylodiimidazole (0.02 mole) was added. The mixture was stirred for 0.5 h at room temperature. Afterwards, the appropriate substituted phenyl– or benzyl– amine (0.02 mole) were added. After 24 h of stirring at room temperature, the product was left in an ice–cold bath and was precipitated with cold water and then purified by crystallization from isopropanol. Physicochemical data, yields, elemental analysis and R_f values are presented in Table 2.

The ^{1}H–NMR and MS spectral data are presented in Table 3.

Pharmacology

Compounds **I** and **IV–XII** were pharmacologically pre–evaluated within the Antiepileptic Drug

Table 4. Anticonvulsant screening project (ASP); phase I test in mice (**I, IV–XII**)

Comp.	Dose	MES[a]		sc.MET[b]		Tox[c]		ASP[d]
	mg/kg	0.5h	4h	0.5h	4h	0.5h	4h	Class.
I	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	1/4	
	300	0/1	0/1	1/5	0/1	1/4	0/2	
IV	30	0/1	0/1	0/1[4]	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1[4]	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
V	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	1/4	0/2	
VI	10	0/1	0/1	0/1	0/1	0/4	0/2	3
	30	0/3	0/3	0/1	0/1	1/8	0/4	
	100	0/1	0/1	0/1	0/1	0/4	0/2	
VII	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	1/1	1/4	0/2	
VIII	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
IX	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
X	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
XI	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	1/4	0/2	
XII	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	1/1	0/4	0/2	

[a]Maximal electroshock test (number of animals protected/ number of animals tested); [b]Subcutaneous pentylenetetrazole test; [c]Rotorod toxicity (number of animals exhibiting toxicity/ number of animals tested); [d]The classification are as follows: 1–anticonvulsant activity at doses 100 mg/kg or less; 2–anticonvulsant activity at doses greater than 100 mg/kg; 3–compound inactive at 300 mg/kg.
Response comments: [4]*death following tonic extension.*

Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Bethesda, by using testing procedures described elsewhere (18,19). Phase I studies of the investigated compounds involved three tests: maximal electroshock (MES), subcutaneous metrazole (sc. MET) and a rotorod test for neurological toxicity (TOX). Phase I involved *i. p.* administration of the compounds as suspension in 0.5% methylcellulose. Phase I was a qualitative assay involving a small number of mice (1–4) at dose levels of 30, 100, and 300 mg/kg. The compounds were classified as the following categories: anticonvulsant activity at 100 mg/kg or less (class 1), anticonvulsant activity at doses greater than 100 mg/kg (class 2), compounds inactive at 300 mg/kg (class 3). The results are given in Table 4.

RESULTS

In this study, we attempted to correlate the anticonvulsant activity of N–phenyl and N–benzyl amides of 2–(3–spirocyclohexanepyrrolidine–2,5–

Table 5. clog *P* values of anticonvulsant drugs a obtained compounds [**I, IV–XII**]

Drugs	clog *P*	clog *P* compounds	No. comp.	Class ASP
Rufinamide	0,54	–0,05	**I**	2
Remacemide	2,27	1,37	**IV**	3
Ameltolide	2,91	1,00	**V**	3
Seretolide	2,99	1,16	**VI**	3
Cerabersat	3,25	3,13	**VII**	3
Harkoserid	2,51	3,08	**VII**	3
Carbamazepine	2,70	2.89	**IX**	3
Progabide	3,14	2,88	**X**	3
Valnoctamid	1,88	2,43	**XI**	3
Fenytoin	1,68	2,38	**XII**	3

dione) acetic acid [**IV–VI**], 4–(3–spirocyclohexanepyrrolidine–2,5–dione) benzoic acid [**VII–X**] and 4–(3–spirocyclopentanepyrrolidine–2,5–dione) benzoic acid [**XI, XII**] with their calculated clog *P* values. All the screened amides were devoid of anticonvulsant activity. Surprisingly enough, the investigated compounds [**IV–XII**] had their clog *P* values in the range from 1.00 to 3.13 the values being comparable with clog P of potent anticonvulsant drugs, ranging from 0.12 to 3.25 (Table 5).

In conclusion, although a 3–spirocycloalkylpyrrolidine–2,5–dine fragment, an amide function, an aromatic area, and selected substituents in the phenyl ring are required for anticonvulsant activity, none of the compounds synthesized in our experiment was active in the tests used.

The obtained results suggest that the anticonvulsant activity of the investigated by us derivatives of 3–spirocycloalkylpyrrolidine–2,5–dione with an amide fragment separated by the methylene group or the phenyl ring at the nitrogen atom cannot be explained by their lipophilicity. We assume that hydrophobicity is the property not only responsible for anticonvulsant activity.

In the nearest future, on the basis of the hitherto obtained results we will synthesize new N–substituted amides of 3–spirocycloalkylpyrrolidine–2,5–dione, in which the substitution pattern and the nature of substituents in the amine aromatic ring will be changed (fluor and methoxy groups by the methyl, chlor, or amine groups, respectively) to optimize the anticonvulsant activity. Our results will be published soon.

Acknowledgements

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